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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/325,602	06/03/1999	ALPHONSE GALDES	CIBT-P02-069	3009

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EXAMINER
BRANNOCK, MICHAEL T

ART UNIT	PAPER NUMBER
1646	28

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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No. 09/325,602	Applicant(s) Galdes
	Examiner Michael Brannock	Art Unit 1646

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1) ☒ Responsive to communication(s) filed on *Dec 26, 2002* .

2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.

3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

Disposition of Claims

4) ☒ Claim(s) *1-27* is/are pending in the application.

4a) Of the above, claim(s) *5-10 and 12-21* is/are withdrawn from consideration.

5) ☐ Claim(s) _____ is/are allowed.

6) ☒ Claim(s) *1-4, 11, and 22-27* is/are rejected.

7) ☐ Claim(s) _____ is/are objected to.

8) ☐ Claims _____ are subject to restriction and/or election requirement.

Application Papers

9) ☐ The specification is objected to by the Examiner.

10) ☒ The drawing(s) filed on *Jun 3, 1999* is/are a) ☐ accepted or b) ☒ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11) ☐ The proposed drawing correction filed on _____ is: a) ☐ approved b) ☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12) ☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13) ☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a) ☐ All b) ☐ Some* c) ☐ None of:

1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____ .
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

*See the attached detailed Office action for a list of the certified copies not received.

14) ☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

a) ☐ The translation of the foreign language provisional application has been received.

15) ☒ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☒ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s). _____
4) ☐ Interview Summary (PTO-413) Paper No(s). _____
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

DETAILED ACTION

Status of Application: Claims and Amendments

1. Applicant is notified that the amendments put forth in Paper 27, 12/26/03, have been entered in full.

2. Claims 1-21 and new claims 22-27 are pending. Claims 5-10 and 12-21 have been withdrawn from further consideration pursuant to 37 CFR 1.142(b), as set forth in the previous Office Action 15, 10/25/00. Further, Applicant is again reminded that claims 1-4 and 11 will be examined only to the extent that they read on the elected species of a method for promoting the in vitro survival of dopaminergic and/or GABAergic neurons wherein said method comprises the administration of Sonic hedgehog, as elected in Paper #6, 8/23/02.

3. Applicant is notified that any outstanding rejection or objection that is not expressly maintained in this Office action has been withdrawn in view of Applicant's amendments.

4. The drawings are objected to as set forth in the attached PTO-948. A proposed drawing correction or corrected drawings are required in reply to the Office action to avoid abandonment of the application. The objection to the drawings will not be held in abeyance.

5. This application contains sequence disclosures that are encompassed by the definitions for nucleotide and/or amino acid sequences set forth in 37 CFR 1.821(a)(1) and (a)(2). However,

this application fails to comply with the requirements of 37 CFR 1.821 through 1.825 for the following reasons: The specification makes reference to specific polynucleotide and polypeptide sequences (see page 49), for example); these references must contain a sequence identifier of the form: SEQ ID NO: X. Appropriate correction is required.

Maintained Rejections:

Claim Rejections - 35 USC § 103

6. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

7. Claims 1-4 and 11 are rejected under 35 U.S.C. 103(a) as being unpatentable over WO 96/17924 to Beachey et al., and/or U.S. Patent No: 5789543 to Ingham et al., in view of Muranishi et al., Journal of Controlled Release, 19:179-188, 1992, as set forth previously on page 5 of Paper 17.

Applicant argues that Muranishi et al. do not suggest the particular lipid modifications required by the claims. This argument has been fully considered but not deemed persuasive. Muranishi et al. specifically teach that the peptides be modified at the N-terminus; they do not teach modification at the C-terminus, see the abstract.

Claim Rejections - 35 USC § 102

8. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless --
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

9. Claims 1-4 and 11 are rejected under 35 U.S.C. 102(b) as being anticipated by WO 95/18856, Ingham et al., 13 July 1995.

Ingham et al., disclose that administration of sonic hedgehog can be used to treat conditions affecting the survival of Dopaminergic neurons in Parkinson's disease and GABAergic neurons as in Huntington's disease (see page 56). Further, Ingham et al., disclose that the sonic hedgehog can modified with a lipid at either the N-terminus or at the C-terminus of the protein (see page 34, first paragraph).

Applicant argues that Ingham et al. do not specifically teach the combination of lipophilic attachments for the treatment of the specific disorders recited in the claims. This argument has been fully considered but not deemed persuasive. As set forth above, Ingham et al. specifically teach that sonic hedgehog proteins can be used to treat conditions affecting the survival of Dopaminergic neurons in Parkinson's disease and GABAergic neurons as in Huntington's disease, and that lipid attachment to the N-terminus is a specific and contemplated embodiment of the invention.

Claim Rejections - 35 USC § 103

10. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

11. Claims 1-4 and 11 are rejected under 35 U.S.C. 103(a) as being unpatentable over Miao et al., J. Neuroscience, August 1, 1997, 17(15)5891-5899 in view off WO 96/29342, Jonassen et al., 26 Sep. 1996.

Miao et al. disclose that sonic hedgehog polypeptides promote the survival of post-induction midbrain Dopaminergic and GABAergic neurons *in vitro* (see the Abstract), such cell types being well known to be lost in Parkinson's and Huntington's disease, respectively. Miao et al., do not mention that the hedgehog polypeptide be modified with a fatty acid moiety or an aromatic hydrocarbon moiety, e.g. derivatives such as phenanthrene, anthracene, naphthalene, naphthacene. Jonassen *et al.* teach the lipophilic moieties such as fatty acid moieties (e.g. page 3) or phenanthrene derivatives (e.g. page 4) are useful for modifying peptide hormones because such modifications protract the action of the peptides (see the Abstract for example). Jonassen teach that the lipophilic moiety be attached to either the N or C-terminal of the peptide see (e.g.

page 2, lines 14-20). Further, Jonassen et al. teach that the particular derivative to use is a matter of routine optimization, depending on the particular disease to be treated (page 7).

Therefore, it would have been obvious to one of ordinary skill in the art, at the time the invention was made, with reasonable expectation of success, to treat diseases characterized by a loss of Dopaminergic and/or GABAergic neurons, e.g. Parkinson's Disease and Huntington's Disease, by administering sonic hedgehog, as taught by Miao et al.. The motivation to do so was provided by Miao et al., who stated that Sonic Hedgehog promotes the survival of post-induction midbrain Dopaminergic and GABAergic neurons (see the Abstract), and particularly protects cultures of Midbrain dopminergic neurons from the toxic effects of MPP+, a specific neurotoxin that induces Parkinsonism *in vivo* (see page 5891, col 2). It would also be obvious to one of ordinary skill in the art at the time the invention was made to modify the sonic hedgehog peptide at the N-terminal with a fatty acid or phenanthrene derivative as suggested by Jonassen et al. when practicing the treatment methods of Miao et al. The motivation to do so was provided by Jonassen et al. who teach that lipophilic modification of peptide protracts the action of the modified peptides (see the Abstract).

Applicant argues that production of hedgehog in Baculovirus does not result in the claimed lipophilic modifications. This argument has been fully considered but not deemed persuasive. Miao et al., also produce hedgehog in E. coli, which results in unmodified hedgehog. Thus, it would be obvious to modify the E. coli produced hedgehog protein as taught by Jonassen

New Rejections:

Claim Rejections - 35 USC § 112

12. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

13. Claims 22-27 rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. The claims require a lipid modification that comprises addition of two or more lipophilic moieties to an N-terminal amino acid residue. There does not appear to be any mention of this embodiment in the specification as filed, and nor would it be reasonably inferred by the skilled artisan that Applicant had contemplated such an embodiment at the time of filing.

14. Claims 1-4, 11, and 22-27 are be rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for the claimed methods comprising administering the N-terminal autoproteolytic fragment of sonic hedgehog wherein the protein is modified at the N-terminal amino acid residue, does not reasonably provide enablement for method comprising the administration of sonic hedgehog modified with a lipophilic moiety at an internal residue, nor for

amino acid sequence variants of SEQ ID NO: 10, 13, 14, 15, nor for fragments of SEQ ID NO: 10, 13, 14, 15. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims. The specification provides no guidance as to which internal residues would be amenable to lipophilic modification. One skilled in the art would appreciate that lipid modification of an internal residue in the polypeptide completely changes the chemical identity of that residue. The specification provides only an invitation to perform random trial and error experimentation to identify which internal residues, if any, are amenable to change. Such extensive experimentation is unduly burdensome. Further, the art recognizes the difficulty in determining the effect of lipid modification on an internal residue, e.g. WO 95/18856 (Ingham et al.) at page 34, Jonassen et al. (e.g. page 2, lines 14-20), Muranishi et al. (see the Abstract) each teach that the lipophilic moiety be attached to either the N or C-terminal of the peptide. Further, the claims require an essentially limitless number of artificially constructed variants of hedgehog proteins, i.e. those that are at least 80% identical to SEQ ID NO: 10, 13, 14, 15, yet the specification has failed to teach which amino acid substitutions/deletions/insertions to make, or which residues of SEQ ID NO: 10, 13, 14, 15 are amenable to lipid modification, to preserve the required function of SEQ ID NO: 10, 13, 14, 15. Nor, has the specification taught which fragments of SEQ ID NO: 10, 13, 14, 15 would work as claimed. The specification has simply invited the artisan to begin an extensive research plan to randomly make and test fragments to try to find fragments that work as claimed.

The problem of predicting protein structure from sequence data and in turn utilizing predicted structural determinations to ascertain functional aspects of the protein is extremely complex. While it is known that many amino acid substitutions are generally possible in any given protein, the positions within the protein's sequence where such amino acid substitutions can be made with a reasonable expectation of success are limited. Certain positions in the sequence are critical to the protein's structure/function relationship, e.g. such as various sites or regions directly involved in binding, activity and in providing the correct three-dimensional spatial orientation of binding and active sites. These regions can tolerate only relatively conservative substitutions or no substitutions (see Bowie et al., 1990, Science 247:1306-1310, especially p.1306, column 2, paragraph 2). However, Applicant has provided little or no guidance beyond the mere presentation of sequence data to enable one of ordinary skill in the art to determine, without undue experimentation, the positions in the protein which are tolerant to change (e.g. such as by amino acid substitutions or deletions), and the nature and extent of changes that can be made in these positions. And nor has the specification provided guidance as to natural variants that may exist that preserve the required function.

Although the specification outlines art-recognized procedures for producing variants, this is not adequate guidance as to the nature of active variants that may be constructed, but is merely an invitation to the artisan to use the current invention as a starting point for further experimentation. Even if an active or binding site were identified in the specification, they may not be sufficient, as the ordinary artisan would immediately recognize that an active or binding

site must assume the proper three-dimensional configuration to be active, which conformation is dependent upon surrounding residues; therefore substitution of non-essential residues can often destroy activity.

Due to the large quantity of experimentation necessary to generate the infinite number of variant recited in the claims and screen same for activity, and the lack of specific guidance as to which internal residues are amenable to lipid modification, the lack of direction/guidance presented in the specification regarding which structural features are required in order to provide activity, the absence of working examples directed to same, the complex nature of the invention, the state of the prior art which establishes the unpredictability of the effects of mutation on protein structure and function, and the breadth of the claims which fail to recite any structural or functional limitations, undue experimentation would be required of the skilled artisan to make and/or use the claimed invention in its full scope.

15. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

16. Claims 1-4, 11 and 22-27 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The claims require lipophilic modification at "an" N-terminal residue or "a" C-terminal residue. The presence of the words "an" and "a" render the claims

indefinite because it is unclear if the claims are referring to "the" N-terminal residue and "the" C-terminal residue or if the claims refer to any residue that might be considered to be in the N-terminus or C-terminus of the protein. If it is the latter case, then the claims are also indefinite because the specification has not set forth which residues make-up the N or C termini.

Double Patenting

17. A rejection based on double patenting of the "same invention" type finds its support in the language of 35 U.S.C. 101 which states that "whoever invents or discovers any new and useful process ... may obtain a patent therefor ..." (Emphasis added). Thus, the term "same invention," in this context, means an invention drawn to identical subject matter. See *Miller v. Eagle Mfg. Co.*, 151 U.S. 186 (1894); *In re Ockert*, 245 F.2d 467, 114 USPQ 330 (CCPA 1957); and *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970).

A statutory type (35 U.S.C. 101) double patenting rejection can be overcome by canceling or amending the conflicting claims so they are no longer coextensive in scope. The filing of a terminal disclaimer cannot overcome a double patenting rejection based upon 35 U.S.C. 101.

18. Claims 1-4 and 11 are provisionally rejected under 35 U.S.C. 101 as claiming the same invention as that of claims 4-14, 18 of copending Application No. 09238243. This is a provisional double patenting rejection since the conflicting claims have not in fact been patented.

Conclusion

No claims are allowable.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Michael Brannock, Ph.D., whose telephone number is (703) 306-5876. The examiner can normally be reached on Mondays through Thursdays from 8:00 a.m. to 5:30 p.m. The examiner can also normally be reached on alternate Fridays.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Yvonne Eyler, Ph.D., can be reached at (703) 308-6564.

Official papers filed by fax should be directed to (703) 308-4242. Faxed draft or informal communications with the examiner should be directed to (703) 308-0294.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Group receptionist whose telephone number is (703) 308-0196.

MB

April 8, 2003

YVONNE EYLER, PH.D
SUPERVISORY PATENT EXAMINER
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